Gathering Momentum for the Way Ahead: The Fifth Report of the Lancet Standing Commission on Liver Disease in the UK

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Executive Summary

Much has been achieved over the past five years in describing the escalating burden of liver disease from lifestyle causes and the impact on hospital and primary care. The section on alcohol in this report reiterates the need for fiscal regulation by Government if overall consumption in the country is to be reduced to improve health, voluntary agreements with the drinks industry having repeatedly been shown to fail. The influence of the industry in its lobbying activities is highlighted in a separate account and myths around the 'nanny state' are also exposed, with the Minimum Unit Pricing (MUP) policy having little influence on average drinkers, affecting mainly heavy drinkers of low cost alcohol products. Results from Scotland following introduction of MUP and with Wales to follow, are likely to seriously expose the weakness of England's position.

Further data on the prevalence of obesity makes the need for a policy on adults even more apparent. The number of people with Type 2 diabetes and its complications continue to rise, as do cases of end-stage liver disease and primary liver cancers from Non-Alcoholic Fatty Fiver Disease (NAFLD). Also covered are the increased risks of co-existing obesity and alcohol as causes of the ten most common cancers, including breast and colon. An in-depth analysis of both NHS and total societal costs is summarised, showing the extraordinarily large sums that could be saved or redeployed elsewhere in the NHS.

On the plus side are the excellent results being obtained with the new antiviral drugs for hepatitis C (HCV) infection, making elimination of chronic infection a real possibility ahead of the World Health Organisation (WHO) target of 2030. Efforts to improve standards of hospital care for liver disease are described and new commissioning arrangements for primary and community care represent some progress in effective screening of high-risk subjects and the early detection of liver disease.

Introduction

In reflecting on the five years of work by the Lancet Commission, one cannot but feel some springs of hope for the future with the substantial progress that has been made. Importantly, the Commission has established a strong evidence base on the disease burden and costs to the country from the lifestyle issues of excess alcohol consumption, obesity and viral hepatitis. Its influence too is evident in the setting up of a Lancet Commission to look at the wider problems of liver disease in Europe and the Global Burden of Disease Study 2016 on alcohol use and burden in 195 countries and territories(1).

A major step forward was the introduction in Scotland of Minimum Unit Price (MUP) policy (from 1st May). Benefits are likely to be evident quite rapidly and it will be difficult for England not to follow suit. When a similar measure was introduced in Canada, alcohol related hospital admissions fell by 14% in the first year, with a 32% reduction in mortality(2, 3). The Commission is also continuing to press for reintroduction of the alcohol duty escalator which was highly effective over the five years it was in place. Successful local campaigns in Southampton, Portsmouth, Nottingham and Tayside are illustrated in this report and there is to be a new Government Alcohol Strategy – but excluding MUP - in 2019. For obesity, the impact of the levy on sugar content of soft drinks that was introduced in April 2018 has already led to reformulation pf products by the industry and the Government has published a strengthened update of its childhood obesity plan (4), making the glaring absence of a strategy for adults ever more apparent.

Encouragingly, the Prime Minister has emphasised that prevention would be at the heart of the new NHS 10 Year Plan(5). The fact that 20% of years of life for those aged 65yrs plus are spent in ill-health, needs to be high on the agenda. Interventions for co-morbidities in older age are often not successful(6), emphasising the importance of preventative measures being carried out before then. Government has also recently announced £300 million from the Industrial Strategy Challenge Fund to support the aging population to *'live longer, better, healthier'*(7). This year's report also includes a critical analysis of the lobbying influence of the alcohol industry and a new financial appraisal.

Alcohol Consumption and Policy Changes

The most recent data indicates that alcohol harm rates in England remain persistently high. In 2016/17 there were 1·1million hospital admissions where the primary or secondary diagnosis was related to alcohol, an increase of 1% from the previous year. For primary diagnoses relating to alcohol only, there were 337,000 hospital admissions, 17% higher than 2006/07. Alcohol related deaths continue to rise. In 2016 there were 5,507 alcohol-specific deaths, 4% higher than 2015 and 11% higher than 2006(8). Of note too is the 20% jump in drink-driving accident deaths in 2016 (up to 240) making the case, already strongly supported, for a reduction in the blood drink-drive limit from 80 to 50mg/100ml (9, 10).

Between 2013/14 and 2017/18 there was an 18% (£162m) reduction in local authority funding for addiction services in England, with 10 local authorities reducing it by ≥40%(11). Over the same period, there has been a 12% fall in the number of people in contact with specialist alcohol treatment and a 19% fall in new alcohol presentations. Services currently reach only 18·3% of the in-need dependent population(12). The situation is further exacerbated by a desperate shortage of addiction psychiatrists.

Comparing alcohol treatment access across the UK, although Scotland has a relatively high rate of ICD-10 F10 alcohol admissions (which are a proxy for prevalence of alcohol use disorders in the general population), the ratio of F10 to treatment access is 1·1. The ratio is higher in other countries (Wales, 1·2; England, 2·4; Northern Ireland, 3·9) indicating lower levels of treatment access compared to Scotland, which highlights the continuing need to upgrade and fund increased capacity of alcohol treatment services across the UK.

Table 1: Specialist alcohol treatment access ratios across the United Kingdom

Country	Number accessing treatment for alcohol only in 2016/17[1]	Number of F10 alcohol hospital admissions in 2016/17[2]	Rate of F10 admissions /100,000 population >18 years, 2016/17	Treatment access ratio (F10 admissions/ treatment access)
Scotland	26,107	27,890	634.6	1.1
Wales	7,890	9,742	390.2	1.2
England	80,454	194,290	444.1	2.4
Northern Ireland	2,577	9,963	694.6	3.9

[1]Excludes concurrent drug misuse as a reason for treatment.

[2]Primary or secondary diagnosis of ICD10 F10 'Mental and Behavioural Disorders due to Use of Alcohol'.

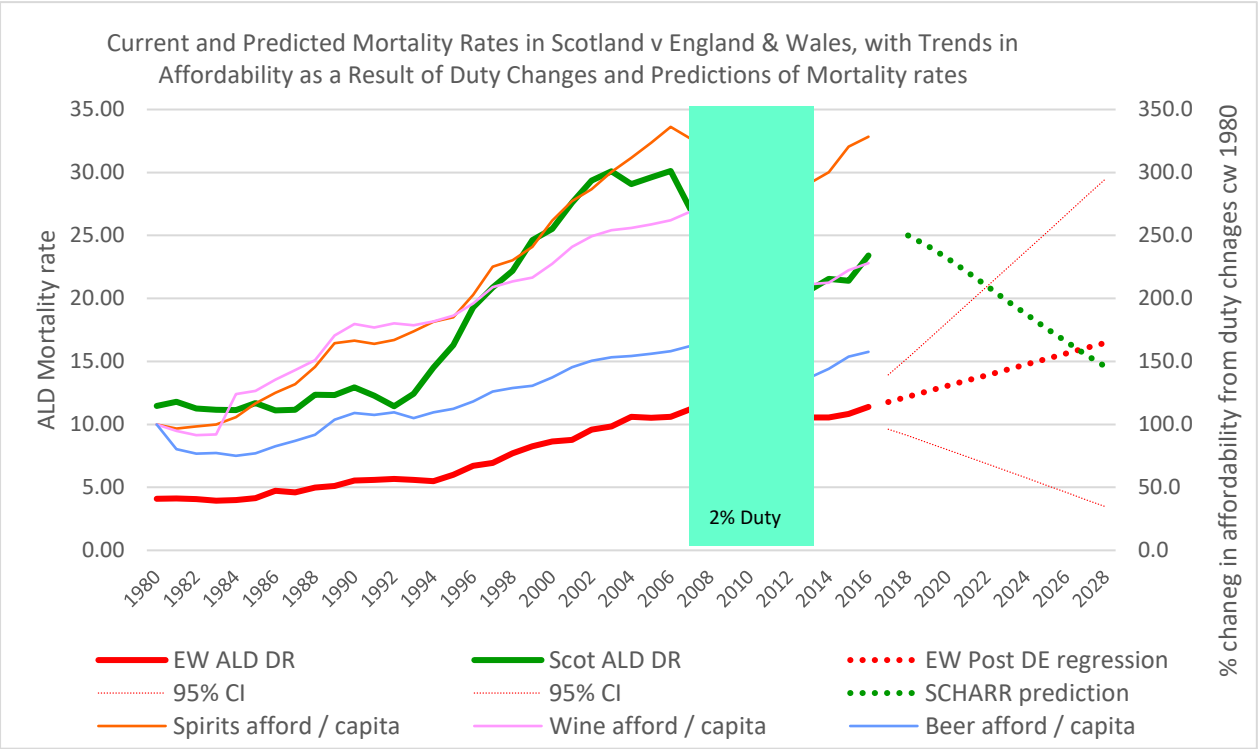
As repeatedly reported, there is overwhelming evidence to indicate that consumption and harm are strongly associated with the affordability of alcohol. Beer sold in shops and supermarkets was 188% more affordable and wine/spirits 131% more affordable in 2016 compared to 1987(13). Despite many calls to take action on cheap alcohol, Government has failed to commit to meaningful measures: the Budget announcement in November 2017 of a new duty band for 'white cider' will do little to increase the price of the most harmful alcohol.

Meanwhile, UK Home Nations have acted, with MUP now in place in Scotland and the Welsh Assembly planning its introduction in 2019, and with the Northern Ireland government having announced plans to introduce MUP before the dissolution of Stormont. The Republic of Ireland, meanwhile, is due to introduce MUP following passage of the Irish Public Health (Alcohol) Bill following a surge in the number of alcohol related deaths costing their health service about £250million a year.

Despite the UK Chief Medical Officers publishing revised low risk drinking guidelines in 2016(14), their promotion has not been a success and many alcohol producers refuse to carry the updated advice on product labels(15). Recent widespread media coverage of the link between drinking alcohol in middle age and a reduced dementia risk was branded by NHS Choices as '*misleading and inaccurate'*(16), whilst a content analysis of alcohol industry funded websites such as Drinkaware found evidence of systematic misrepresentation of the evidence linking alcohol to an increased risk of cancer(17).

The announcement that £20billion funding has to be found to support the NHS has added pressure on Government to assess its revenue raising options, including increases in duty on alcohol(13). The projected costs to the Exchequer of successive alcohol duty cuts between 2013/14 and 2022/3 are £8.345 billion(18), equivalent to the annual salary of 318,000 nurse practitioners(19). Alcohol duty increases need not impact economic productivity adversely, as is often claimed by industry representatives. A 10% increase in UK alcohol duties is estimated to boost GDP by £847 million and create 17,000 full-time equivalent jobs, if revenue raised is redirected to public services(20). Furthermore, alcohol duty cuts do little to assist the pub trade, successive surveys of pub landlords identifying cheap supermarket alcohol as one of the biggest threats to their trade(21, 22).

Figure 1: Mortality rates from alcohol related liver disease in England & Wales and Scotland from 1980-2016.



Impact of duty changes on affordability has been calculated using the methodology in Statistics on Alcohol 2018(23). Duty increases for spirits commenced in 2007 and the inflation duty escalator for most alcoholic beverages was in place between 2008 and 2013. Predictions of mortality rates in England and Wales are a linear regression of data after the duty escalator, the wide 95% confidence interval reflects the paucity of data points. Predictions in Scotland following the introduction of MUP are estimated using the School of Health and Related Research, University of Sheffield (SHARR) predictions on deaths in harmful drinkers(24). Analysis by Professor Nick Sheron.

Countering the Lobby of the Alcohol Industry

Almost a quarter of the alcohol industry's sales are consumed by just 4% of the population drinking at harmful levels and two thirds of its revenue comes from those drinking above the recommended guidelines(25). As health policy has shifted from largely ineffective measures such as health education to concentrate on measures addressing price, availability, and marketing, the industry has stepped up its engagement in policy debates. This change reflects growing attention to what have been termed the *"corporate determinants of health"*(26) in which powerful industries seek to shape the policy discourse, in particular by defining which measures governments can legitimately adopt, invoking terms such as the "nanny state".

The industry seeks to frame alcohol-related harm as a matter of individual choice rather than a health issue: *"ultimately, it is the individual who makes the personal decision to drink responsibly or irresponsibly"* and strives to differentiate *"responsible"* from *"irresponsible"* or *"problem"* drinking, while avoiding attempts to define them(27, 28). Industry also seeks to shift attention away from those measures that, while most effective, threaten its interests(29). A systematic review of pledges by the alcohol industry within the United Kingdom Public Health Responsibility Deal (PHRD), a public private partnership, found that most were likely to be ineffective in reducing consumption(30) or had not been implemented(31). Nonetheless, the industry routinely emphasises public-private partnerships as the most effective way to reduce alcohol-related harm: *"we strongly believe that a system of co-regulation is the most appropriate and effective approach"*. Similarly, industry emphasises the importance of public-private partnerships at local level, even though the primary motivation is to enhance their reputations(31) and a review of Community Alcohol Partnerships with local government found scant evidence of effectiveness(32).

These tactics echo those traditionally used by the tobacco industry, with which several major alcohol producers have collaborated to influence norms on scientific methods to their advantage(33). Recent studies of the tobacco(34) and food industries(35) have shown that, despite having access to the same body of evidence, industry responses often reach quite different conclusions to those of health and scientific bodies. The extent to which policies promoted by the alcohol industry align with those favoured by public health, by crime and public safety organisations and by local government is presented graphically in Table 2 (full details in Appendix 1). Large positive values, coloured green, represent views in favour of a solution. In health submissions, MUP scores plus 110, indicating strong support, while in industry submissions it scores minus 59, signifying strong opposition. Many of the policies supported most strongly by public health organisations which are also likely to be most effective, such as those related to price(36), are strongly opposed by the industry while those favoured by industry, such as public-private partnerships and self-regulation are largely ineffective and attract little support from the other organisations. There is also an extensive literature on how links are frequently concealed(26). Supposedly independent responses from think tanks that conceal their funding(37) and some trade associations that align with industry views, should be treated with great suspicion.

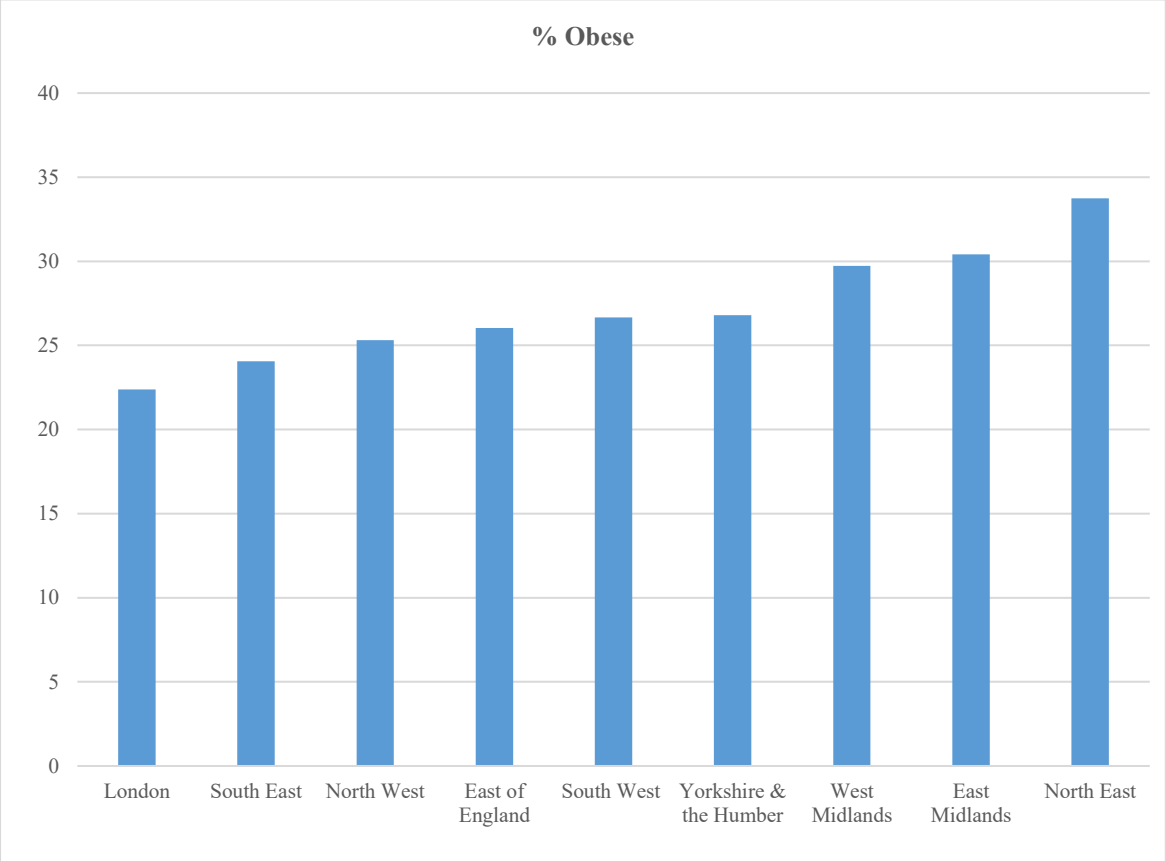
Table 2: Summary of responses; positive/green values in favour, negative/red values opposing (* = joint ranking)

		Health Composite - rank		Crime and public safety		Alcohol industry		Council / Local Authority	
		Score	Rank	Score	Rank	Score	Rank	Score	Rank
Taxation and price regulation	Implement a MUP	110	1	29	1	-59	1	52	1
	Ban multi-buys and/or price promotions	90	2	22	3	-33	5	34	2
	Ban sales below cost/loss leaders	66	3	11	8	11	17	31	4
	Increase/amend tax/consistent price per volume	58	7*	6	11	-7	18*	18	9
Regulate marketing	Regulate marketing	55	9	4	15*	-7	18*	10	16
	Self-regulation of marketing	-34	14*	-1	21	31	7	-6	18
Regulate availability	Control the spatial and temporal availability of alcohol	61	5	24	2	-16	13*	25	6
	Health as a licensing objective	59	6	20	4*	-16	13*	18	10
	Restrict the location of alcohol in licensed premises/separate alcohol checkouts	31	16	2	19*	-26	9*	15	11
	Age verification/test purchasing	65	4	20	4*	56	2	32	3
	Increase the drinking age from 18 to 21 years	19	19	-2	19*	-32	6	-12	12*
Provision of information and education	Provide information/education	43	13	5	14	46	4	19	7*
	Point-of-sale information/labelling	58	7*	13	7	17	12	19	7*
	School and higher education-based programmes	28	18	7	10	27	8	12	12*
Preventing drink-driving	Actions to prevent or reduce drink-driving	30	17	3	17*	5	20	2	20
Interventions	Identification and brief advice/treatment	52	10	5	13	12	15	7	17
	Family interventions/parenting programmes	51	11	6	12	26	9*	28	5
Alternative beverages	Lower strength alcohol	46	12	16	6	11	16	11	14*
	Soft drinks should be cheaper than the cheapest alcoholic drink	34	14*	8	9	0	21	11	14*
Partnership working	Government/industry partnership approach	5	21	3	17*	52	3	1	1
	Responsibility deal	-8	20	-4	15*	20	11	-3	19

Obesity Prevalence and Consequences

While the overall prevalence of obesity has remained broadly stable across the United Kingdom over the last few years, this masks widening inequalities in terms of socioeconomic status, geography and severity. The most recent statistics come from the 2016 Health Survey for England(38), which shows that 40% of men and 30% of women are defined as overweight, while 26% of men and 27% of women are obese, with the highest prevalence in the North East (Figure 2).

Figure 2: Prevalence of obesity by region of England (Health Survey for England 2016)



Stark socioeconomic differences are most marked in children. Data from the National Child Measurement Programme show that the difference in prevalence between the most and least deprived deciles has increased since 2006/7, from 4·5% to 6·8% for the 4-5 year old children in Reception year and from 8·5% to 15·0% for 10-11 year olds in Year 6 (38, 39).

The second iteration of the Government's Child Obesity Plan published in June 2018(40) currently under consultation, adds proposals to restrict advertising and marketing of unhealthy foods before 9pm, align regulation between broadcast and social media, introduce calorie labelling for the out-of-home food sector, and end price promotions of unhealthy products. Together with the Sugar Drinks Industry Levy introduced in the 2016 Plan, the new proposals send a clear message from Government that the unhealthy food environment needs to change.

In England, the rate of non-alcoholic steatohepatitis (NASH) in patients with and without diabetes has continued to rise(41) as do diagnoses of Type 2 diabetes and the risk of hospital admission or death for chronic liver diseases(42). In combating rising obesity levels, the further actions required include greater powers for local authorities to alleviate poverty and to create healthier environments in towns and cities, thereby tackling some of the factors that contribute to the condition known by doctors as 'Shit-life' Syndrome(43).

The provision of services to support people who are already obese is a continuing major gap alongside the provision of bariatric services which continue to lag behind the clinical demand. Whereas obesity rates have continued to rise over the past 5 years, according to National Bariatric Surgery register data there has been no

increase in bariatric operations, despite compelling evidence of their cost-effectiveness. The figure for surgeries performed reached a plateau in 2013 with only 6362 performed in 2017, down from 6447 in 2016(44). A recent paper highlights the low numbers of procedures undertaken in the UK compared with other European countries: 6,590 primary bariatric/metabolic procedures were performed in the UK in 2016, in comparison with 53,547 in France and 14,863 in Italy, two countries with broadly similar population size(45).

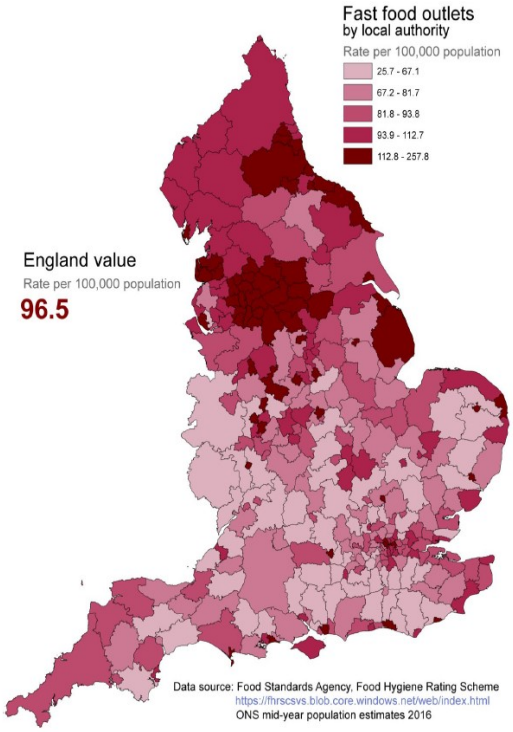


Figure 3: Density of fast food outlets 31/12/2017
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Ongoing Work of Public Health England (PHE)

In identifying characteristics of areas with the highest risk for liver disease, coastal towns, resorts and ports have emerged as some of the most likely areas. 12 of 20 top local authorities (LAs) for alcohol licenced premises were coastal towns that share similar features of deprivation, a night-time drinking economy and high levels of drug misuse. 60% of variability in rates of premature liver disease across England's lower tier LAs can be explained by levels of deprivation, and 45% of premature mortality from alcoholic liver disease in 2014-16. A recent publication by PHE showed the association between areas of deprivation and density of fast food outlets, these areas also having high rates of obesity and excess alcohol consumption (Figure 3). PHE is continuing to update regularly the Local Authority Liver Disease Profiles and Local Alcohol Profiles. It is also working with NHS RightCare and other clinical stakeholders on a liver disease pathway and a range of liver-related spending/outcome indicators that can be accessed via local CCG leads. PHE is also producing Sustainability and Transformation Partnership (STP) packs which bring together data and advice on more complex disease management and will emphasise the need for more patients to access specialist services.

Elimination of Chronic HCV and HBV Infection

The development of oral, highly effective therapies for chronic HCV infection encouraged the WHO to promote worldwide elimination of chronic HCV infection by 2030(46). Lord O'Shaughnessy, Parliamentary Under-Secretary of State at The Department of Health, confirmed in January 2018 that England will work towards elimination with the aim of being one of the first developed countries to eliminate HCV. The regional operational delivery networks (ODNs) that were set up specifically for this purpose have proved highly effective and reports from the national registry in early 2018 showed that 35,634 infected patients were registered, with 27,360 patients treated. Of the 15,000 treated patients with recorded outcomes, over 90% had achieved viral clearance although response rates in patients with genotype 3 and cirrhosis were slightly below 90% (47).

Challenges remain in identifying cases of hitherto unrecognised chronic HCV infection. A novel business deal linking numbers cured to HCV treatment procurement, is currently being negotiated with the pharmaceutical industry to facilitate the significant investment in case finding needed. At present, if the initial therapy does not eliminate the virus, patients are offered re-treatment with salvage therapies but those who are re-infected or have acute disease, particularly in the context of drug addiction, are not eligible for re-treatment. Allowing these patients to access repeated therapy will reduce the risks of onward transmission from a persisting pool of subjects with chronic infection.

For chronic hepatitis B virus (HBV) infection, the recent introduction of universal immunisation for children will reduce the prevalence of infection in the long term. New drug regimens with novel immunomodulators and innovative direct acting anti-viral agents (DAAs) are being explored in clinical trials and many are optimistic that functional cure, with HBsAg clearance, will be achievable for many cases within the next five years. As with HCV, case finding for currently unidentified subjects with HBV is crucial. The presence of a hepatitis C elimination programme also has the potential to facilitate HBV diagnosis and access to treatment, and together to

reduce the risk of developing cirrhosis and liver cancer. The lifetime risk of HCC in HBV infected men from Taiwan is as high as 25%(48). In the UK, risk is likely to be highly variable depending on multiple factors including race, viral genotype, country of birth and comorbid factors of alcohol and obesity.

Extent of Attributable Cancers

In 2015, the lifetime risk of a person born after 1960 developing cancer had reached >50% (49). Over half of UK adults who are currently under the age of 65 will be diagnosed with cancer at some point in their lifetime. Studies globally have shown that between 30-50% of all cancer incidence is preventable(50). In the UK almost four in every ten cancers diagnosed are a result of behavioural and/or environmental factors(51). Tobacco use along with overweight and alcohol are the highest preventable causes, with alcohol consumption causing 11,900 cases of cancer each year(51). In 2016 the Chief Medical Officers within the UK published updated guidelines that emphasised the risk of increased levels of drinking including the link to cancer(14) and the International Agency for Research on Cancer (IARC) has labelled alcohol as a Class I carcinogen (the same category as tobacco)(52).

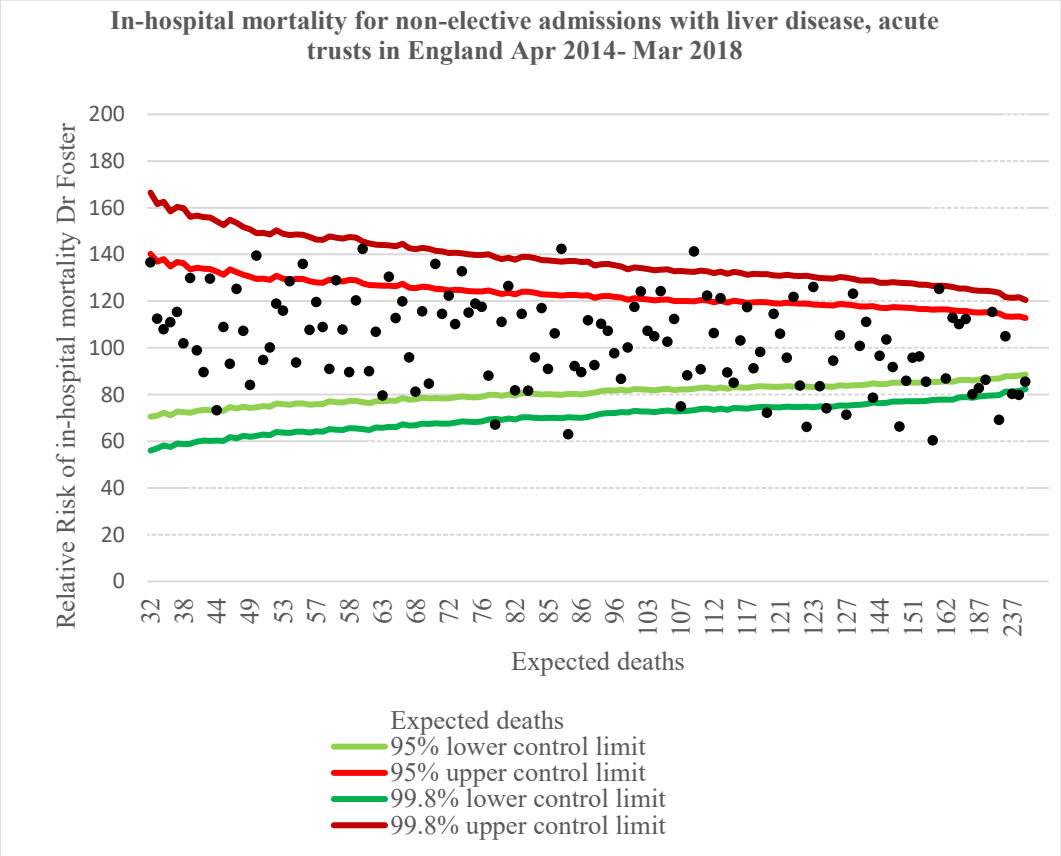
Alcohol is associated with ten different types of cancer including liver(53), yet only one in ten members of the public are aware of this link and even when informed, do not realise that these include breast (one of the most common; 4,400 cases/year attributable to alcohol) and bowel (one of the hardest to treat if not diagnosed early; 2,500 cases/ year attributable to alcohol)(51, 53, 54). The combined behaviours of smoking and drinking alcohol have also been found to increase an individual's risk of cancer especially those of the mouth and throat (53). In England alone, it is estimated that if current drinking trends continue, alcohol consumption will be responsible for 135,000 cancer deaths and £2billion in cancer costs to the NHS by 2035(55).

Approximately 48% (2,800) of primary liver cancers in the UK could be prevented each year, with overweight and obesity being responsible for 1,300 cases and alcohol harm 400(51). More policy attention needs to be directed at factors driving unhealthy behaviours including alcohol, obesity and tobacco which increase the burden of preventable diseases on individuals and the NHS.

Variations of In-hospital Mortality in Non–elective Admissions for Liver Disease

The team at Dr Foster (www.drfoster.com) have provided the Commission with comparative analysis data of in-hospital mortality for liver admissions to hospital trusts in England from April 2014 to March 2018 using the diagnosis groups: "liver disease, alcohol-related" and "other liver disease". 17 trusts had a significantly lower relative risk of mortality (95% control limit), ten of these being at the 99·8% limit, whereas 19 trusts had a significantly higher relative risk of mortality (95% control limit) with two trusts above the 99·8% control limits (Figure 4), (the full dataset from Dr Foster is included in Appendix 2, *online report only*). Although some of these findings may be due to natural variation when adjusted for a variety of confounding factors the crude % mortality rate ranged from 6·1% for the best performing trust to 16·3% for the worst(56). This worrying variation in outcomes provides further support for the National Confidential Enquiry into Patient Outcome and Death (NCEPOD), as well as the NCEPOD report on Care of Patients who had a Severe Gastrointestinal Haemorrhage which raised concerns previously about the management of alcohol related liver disease, reporting that(57, 58): *"The care of patients who died with a diagnosis of alcohol-related liver disease was rated as less than good in more than half of the cases reviewed."*

Figure 4: Funnel plot of the relative risk of in-hospital mortality for non-elective liver admissions (liver, alcohol and liver, other) from Apr 2014-Mar 2018 for 134 acute trusts in England.
Relative risk (RR) is a ratio of the observed number of negative outcomes to the expected number, multiplied by 100. The benchmark figure is 100; values greater than this represent performance "worse" than the benchmark, and less than 100 "better". RR has to be interpreted in the light of the accompanying confidence or control limits; outside the 99.8% control limit, the likelihood of variation being due to chance is around 1:1000. In the most recent data from April 2017 – Mar 2018, some the trusts which were previously outliers have improved their mortality figures. The full table of results and the methodology for calculation of relative risk and control limits are given in Appendix 2. Data was kindly provided by Matthew Parry (www.drfoster.com).



NCEPOD made a series of detailed recommendations and the Royal College of Physicians (RCP) has established an accreditation scheme for hospital care – Improving Quality in Liver Services (IQILS)(59). After units have signed up, they work through two levels of standards, with a visit before accreditation by a team comprising a doctor, nurse and patient who decide if the service can be accredited. The scheme has been active for one year and so far, 33 services have signed up from England and Wales and are working towards accreditation.

The Hepatobiliary Clinical Reference Group(60), using Hospital Episode Statistics (HES) data, have found that a number of trusts are inappropriately receiving liver tariff funding; 95·2% of admissions are in 40 of the 100 plus trusts. A new hepatology service specification has been developed alongside new metrics to monitor the performance of trusts providing liver services. The overall plan is the adoption of a 'hub and spoke' service model, with more complex patients being appropriately referred to centres that are able to provide specialised liver care at all times.

Complementing this, is a survey of hospitals in the UK by the British Association for Study of the Liver (BASL) on current hepatology staffing and facilities for in-patient care. Within England, this information will be correlated with clinical activity levels based on coding and HES data, with regional prevalence data and mortality statistics derived from Public Health England (PHE) and Dr Foster data.

Figure 5: Map illustrating sites of registered IQILS services (as at 6th August 2018)

Primary Hepatocellular Carcinoma (HCC): Incidence and Survival

Between 2007 and 2016, HCC incidence annual rates in England increased (5·6 to 8·8 and 1·4 to 2·2 per 100,000 in men and women respectively), in parallel with frequency of chronic liver disease - an average annual percentage (AAPC) increase of 5·9% (95%CI 4·7-7·2) in men and 6·5% in women (95%CI 4·9-8·2). Mortality rates increased only slightly more slowly than incidence rates but between 2005-2006 and 2015-2016, 1-year net survival increased from 27·3% to 44·4% and 30·0% to 45·8% in men and women, respectively (Figure 6).

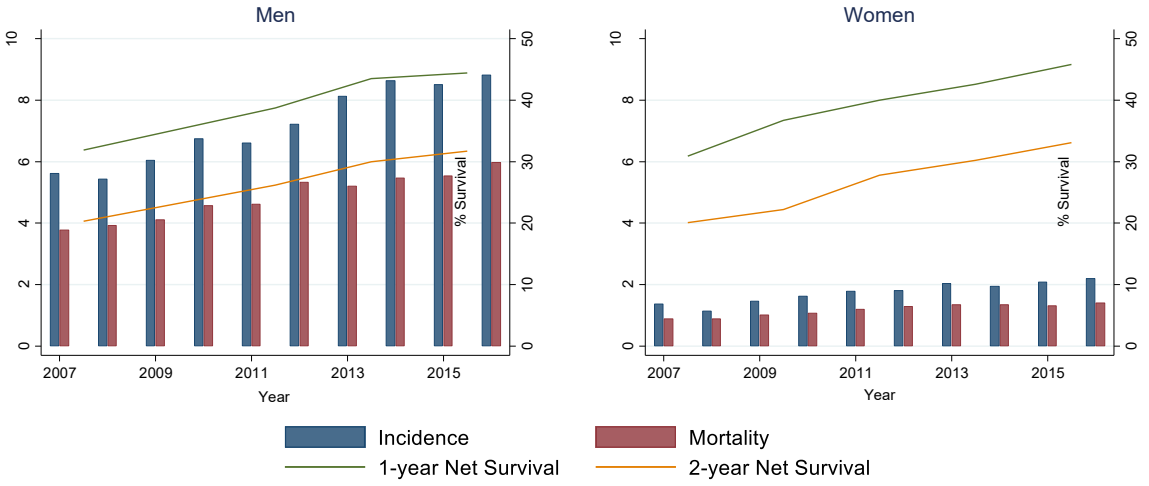


Figure 6: HCC Incidence, mortality and survival 2007-2016
European age-standardised incidence and mortality rates per 100,000 persons per year and International Cancer Survival Standard (ICSS) age-standardised 1-year and 2-year net survival per 2-year period. The 2015-2016 figure is based on preliminary data and likely to be underestimated.

The route to diagnosis is strongly associated with survival. Emergency presentation remains the most common mode but between 2006 and 2015 fell from 43·4% to 34·0%, whereas GP and Two-Week Wait referrals, which have a better prognosis, increased (from 24·0% to 30·0% and 6·2% to 13·6% respectively)(61). Although survival is improving, late diagnoses remain alarmingly common. The majority of patients currently cannot be offered curative therapy and increasing the focus on early diagnosis is essential.

Liver Transplantation: Increased Numbers and Organ Donation

Over the last seven years there has been a 50% increase in the number of transplants performed (from 675 to 1014) and the size of the waiting list has fallen from a peak of 611 in 2014/5 to 359 at the end of the 2017/8 year, the latter reflecting the reduced numbers with HCV liver disease requiring transplantation. Outcomes are comparable across all centres with one-year survival rates around 95% for elective liver transplantation.

A new allocation system for elective adult liver transplantation was launched in March 2018. Developed over a period exceeding five years, it is based on complex methodology that reflects likely transplant benefit from the liver graft on offer, with the patient's disease characteristics. Allocation is national rather than regional and delivers on an objective that the organ will be directed to the individual considered most likely to benefit from it. Initially restricted to organs retrieved after brain death, the intention after six months is to include all organs unless there are indicators that the utilisation of organs retrieved after cardiac death would be negatively affected.

The potential for machine perfusion technologies to improve organ quality is beginning to be realised. A landmark study of normothermic perfusion, led by Professor Peter Friend, recently confirmed benefit in a randomised controlled study with a 50% lower level of graft injury(62). The potential with this to expand the donor pool is tantalising, particularly for organs donated after cardiac death. The contribution of these organs to the donor pool has remained static over the last six years at around 20% and currently there is a high discard rate. Importantly, a continuation of the increase in the number of organs becoming available would allow some relaxation of the indications considered acceptable for transplantation in hepatocellular carcinoma, as well as an opportunity to explore new indications e.g. in cholangiocarcinoma.

Detection by Screening of Liver Disease in Primary Care

The Royal College of General Practitioners (RCGP) and British Liver Trust (BLT) partnership has re-iterated its commitment to driving forward the screening of high-risk patients, with a major focus on synthesising national guidelines and evidence based practice and providing clear recommendations for decision makers and GPs. The Liver Disease Toolkit is available online (http://www.rcgp.org.uk/clinical-and-research/resources/toolkits/liver-disease-toolkit.aspx) and information is also being delivered through four regional workshops for GPs and a commissioning working group to disseminate a 'pathway to action' resource nationwide. The resource will highlight the evolving liver disease epidemic to commissioners and the need to engage in developing local pathways under the headings 'finding your patients at risk', 'assessing for fibrosis/cirrhosis' and 'robust systems for follow up'. It will be disseminated widely by the end of 2018. The incorporation of a liver health check into already routine practice (e.g. the NHS health check, annual diabetic and hypertension reviews) will also be encouraged.

Engaging GPs and commissioners, particularly in England where decision making is so fragmented, is a major challenge and continues to be a priority. Possible solutions include incentivising secondary care engagement directly with clinical commissioning groups (CCGs) to drive forward case-finding pathways. Inspiring local GP champions, direct access to transient elastography equipment for measuring fibrosis (Box 1 and 2), and 'intelligent' central laboratory IT reporting systems for enhancing the value of liver function tests (Box 3), as well as multi-agency strategies (Box 4), have all been shown to work. Transforming these examples of 'best practice' into 'normal practice' would represent a huge shift forward in the detection of liver disease at an early stage.

Box 1: Case Study - Southampton Projects on Detection of Liver Disease
The LOCATE(63) study categorised 910 subjects from five practices into a simple matrix of aetiology versus stage of fibrosis/cirrhosis using both transient elastography and the liver traffic light (collagen p3np, hyaluronate and platelet count)(64) and found 44 new cases of cirrhosis and 141 with progressive fibrosis. Positive or borderline results were followed by a behavioural warning intervention.

A new liver pathway based on the 2014 Lancet primary care pathway(65), similar to the recent BASL/BSG guideline(66), promoted to GPs by Dr Mead Matthews, a 'LOCATE GP', resulted in a paradigm shift, with GPs now requesting liver fibrosis markers directly and referring patients to hepatology clinics on the basis of the stage of fibrosis as opposed to an elevated ALT. The pathway has been adopted city wide and the CCG have commissioned direct access transient elastography based on primary care.

Box 2: Case Study – Scarred Liver Project, Nottingham
Developed out of a pilot project in 2015, this fully integrated CCG commissioned pathway is now in place across Greater Nottingham. It is accessible to more than 100 GPs serving a population of approximately 700,000 people. GPs identifying patients with hazardous alcohol use or Type 2 diabetes can, via their standard IT platform, request transient elastography. Patients are counselled with a brief intervention at the time of their scan before results and recommendations are returned to the referring GP. The pathway has been demonstrated to be cost effective (incremental cost effectiveness ratio [ICER] per quality adjusted life year [QALY] £2,138 for NAFLD and £6,537 for ALD) and has seen over 2000 patients in 18 months since full implementation in September 2016(67, 68).
https://www.scarredliverproject.org.uk/

Box 3: Case Study – Tayside, intelligent LiverFunctionTesting (iLFT)
Scottish Government supported research funded development of an automated investigation algorithm which maximises diagnosis and management.

1. GP requests LFTs via electronic system, entering data about patients' alcohol consumption, BMI and features of metabolic syndrome.
2. In the laboratory, the finding of abnormal LFT results triggers an automated cascade of additional tests on the same sample to find an cause (viral serology, liver immunology, iron studies, alpha 1 anti-trypsin, and caeruloplasmin) and stage fibrosis (Fib 4 and NAFLD fibrosis score) This information automatically populates diagnostic algorithms and management plans.
3. The report is made available to the GP in real time for them to action. Access to the management plans is delivered electronically as web hyperlinks.

In a trial of iLFT, the diagnosis rate was increased by 43% and it was cost-effective, with a saving to the NHS of £3,216 over a patient lifetime. It is now being rolled out in other sites across Scotland.

Box 4: Multiple Agency Strategy in Portsmouth

In 2013 Portsmouth had:

- Highest alcohol-related admissions in South East England
- Prolonged inpatient stays and high readmission rates
- Cirrhosis rate double national average
- Population in worst quintiles for obesity, alcohol misuse and viral hepatitis
- High density of retail outlets selling cheap alcohol

Key multi agency solutions by the NHS Trust, City Council and local CCGs:
These included Brief Advice in community pharmacies (7,500 per year) using "alcohol scratchcard"; "Reducing The Strength" campaign to withdraw cheap beers and ciders of >6·5% alcohol; Specialist Alcohol Nursing Service, delivering 98% of "detoxes" on an outpatient basis; universal screening of admissions for alcohol misuse(69); electronic early warning scores to identify deteriorating inpatients(70).

Achievements over subsequent 5 year period:

- More patients accessing alcohol treatment
- Fewer hospital admissions
- Significant fall in community outlets selling cheap alcohol (from 167 to 53)
- Nurse-delivered outpatient detox completion rate of 99%
- Significant net savings for the local NHS economy

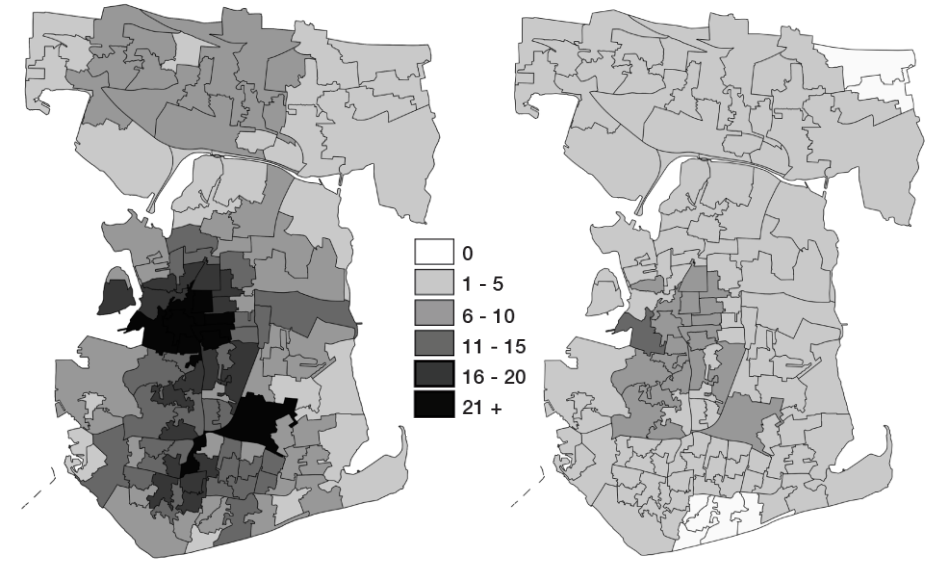


Figure 7: Change in Number of Outlets in Portsmouth selling Super Strength Alcohol (SSA), per 1000 inhabitants aged ≥18yrs 2012-2016 (data courtesy of Rob Anderson-Weaver, Portsmouth City Council).

Remaining Priorities for Paediatric Liver Disease

The Commission has successfully emphasised the need to improve early diagnosis of neonatal liver disease, implement immunisation programmes to prevent transmission of hepatitis B and to treat hepatitis C while strengthening transitional arrangements from paediatric to adult care. Remaining priorities include the rapid increase in Non-Alcoholic Fatty Liver Disease (NAFLD) in children and the long-term outcome of children after liver transplantation.

Non-alcoholic Fatty Liver disease (NAFLD)

Prevalence has increased along with childhood obesity (Table 2)(39), estimates suggesting that it affects 12·9% (95% CI: 10·0-16·5%) of 10-11 year olds in England, with higher rates in adolescents(71). Up to 30% could have either non-alcoholic steatohepatitis (NASH) or fibrosis, equating to >150,000 affected children in the UK(72, 73). Most children are undiagnosed and only a minority are referred for investigation of abnormal liver function tests or steatosis on ultrasound. The three national paediatric units had 353 cases referred over a 2-year period, at a median age of 13 years. This is to be compared with an estimated total number of 654,153 children with NAFLD in the UK aged between ten to 16 years.

Children have the same outcomes as in adults including cardiovascular disease, Type 2 diabetes and non-hepatic malignancy, followed by liver disease(74) but to date there is no prospective data to assess this. A retrospective study of 66 children with NAFLD reported transplantation in two patients within 20-years and a 9% prevalence of Type 2 diabetes after 11-years of follow-up(75). Healthy young adults (18-20 years) with obesity have an increased all-cause liver-related mortality after 25-years(76). Early evidence of atheroma formation, reflected by increased carotid intima media thickness(77) has been demonstrated and a diagnosis of metabolic syndrome in 12-years olds (50% of whom may have NAFLD), shown to increase their risk of cardiac events over 25-years(73, 78). The European Paediatric NAFLD Registry(79) has recently been established to prospectively address the effects of NAFLD.

Table 3: UK paediatric NAFLD figures

	Reception (4-5yrs old)	Year 6 (10-11yrs old)
% overweight/obese	22·6%	34·2%
% obese	9·6%	20·0%
% with NAFLD		12·9%

Prescription Charges, a Potential Risk Factor for Poor Adherence to Immuno-suppressive Medication in Young Adults

Research carried out by the Prescription Charges Coalition found qualitative evidence these can have a significant impact on medicine adherence. 85% of 160 articles reported that higher cost was significantly associated with a decrease in adherence (80). Young people may be particularly affected by financial charges due to lower income, particularly those who remain in full-time education after the age of 18 years when they are no longer exempt. In a sample of young patients with liver disease from one of the paediatric liver centres in England (n=80), less than a quarter (21%) were in full-time employment, with 74% still being in full-time education. When coupled with factors inherent to the developmental period of adolescence (e.g. feeling 'invincible', increased risk-taking behaviour), young people may not prioritise the purchase of medication prescriptions. A meta-analysis conducted in the USA(81) found that patient adherence was improved in patients who received medication at reduced or no cost. The long-term financial consequences of individuals being unable to afford their medication is likely to be far greater for the NHS and wider economy than the estimated £360-430 million cost (less than 0·5% of the NHS budget) in providing free prescriptions for patients with long-term conditions(82).

New Financial Appraisal and Sustainability of NHS Funding

The Lancet's fourth report(83) and Foundation for Liver Research's 2017 financial analysis(84) found the costs to the NHS of alcohol misuse and obesity were £3·5bn and £6·1bn per year respectively (and escalating) – substantial sums in the context of Government's commitment to an extra £20bn per year by 2022-23. Full societal costs for alcohol abuse including crime, lost productivity and child services were estimated to be considerably higher, at £21billion per year in England and Wales, although more recent studies had suggested £27 billion and even as high as £52 billion. For obesity, the total cost to society was £27 billion per annum with some estimates as high as £45 billion.

The most recent financial appraisal by the Lancet Commission in August 2018 entitled: *"Understanding the Importance of Living Well for Longer"* included further analyses and confirmed the long-term financial benefits of measures to tackle alcohol misuse and obesity. A 50p MUP policy for alcohol would lead to a cumulative ten-year reduction of alcohol-attributable hospital admissions of 35,100 cases and societal savings of £2·692bn. Restoration of the alcohol duty escalator would result in 10,314 fewer alcohol-attributable hospital admissions and 544 fewer deaths each year after ten years (85). The new duty band for higher strength cider is too small a step and the most impactful measures for reducing alcohol consumption remain the MUP and the alcohol duty escalator.

Over twenty years, lowering the sugar intake of sugar-sweetened beverages by 40% would reduce cases of type 2 diabetes by up to 309,000, with 14,848 fewer associated cases of cardiovascular complication. Cutting calorie intake of existing overweight and obese 4-64 year olds by 20% would prevent 35,370 premature deaths and save £9·020 billion in health and social care costs over 25 years.

The continuing development of NHS England's 10 Year Plan, triggered by Government's new multi-year funding settlement, offers a major opportunity to include serious consideration of the cost of lifestyle factors as well as of the disease burden.

Progress in the Devolved Nations

Scotland

Previous Commission reports highlighted increases in chronic liver disease mortality between 1993 and 2003 and between 2003 and 2012 there were falls in mortality in association with a decrease in consumption of around 9%. The latter was most likely due to a combination of a fall in incomes after the financial crash and rising alcohol prices (Figure 3). One possible explanation for the marked fall in the amount of alcohol sold at very low prices (under 40p) between 2009 and 2013(86) is that the alcohol industry was adapting to the potential introduction of MUP. Since 2012, however, affordability has increased again and alcohol related mortality, including deaths from liver disease, has begun rising in Scotland(87). Liver disease, which represented 40% of alcohol related mortality in 1982, had risen to over 80% by 2016(48).

The introduction in Scotland on 1st May 2018 of MUP followed a ruling by the UK Supreme Court that the Scottish Government had properly analysed the likely impact of the measure and was entitled to conclude that it would benefit health, particularly in low income groups(88).

The Alcohol Brief Intervention (ABI) programme introduced in 2008 continues in Scotland with over 86,000 ABIs delivered in 2017, predominately in primary care(89). National guidelines by the Scottish Health Action on Alcohol Problems (SHAAP) recommend the addition of liver fibrosis screening for those receiving ABI. The guidelines also advocate the development of "acute alcohol teams" with assertive follow up for those with the physical complications of alcohol excess.

HCV treatment continues to be prioritised, working towards its elimination within the WHO deadline of 2030. In the short term, this is dramatically reducing the infection as a cause of end-stage liver disease and HCC. Scotland is using Tayside as a test bed for the rapid escalation of HCV treatment among people who use injection drugs, to determine if "treatment as prevention" works and is cost-effective, which would be a vital tool in the rapid elimination of HCV.

Wales

The Liver Plan(90) first introduced in 2015 has overseen considerable progress in provision of Alcohol Care Teams, treatment of blood borne viruses (BBVs) and organisation of liver services. Since 2014 there has been a 70% increase in hospital based alcohol liaison nurses and four of six health boards now have an alcohol lead. Wales was also the first to remove restriction on access to direct acting antivirals (DAAs). All those waiting for DAAs had been treated by 2017.

Importantly, the Welsh Government has passed a Public Health Act(91) mandating an Obesity Prevention Strategy, and a Minimum Unit Price for Alcohol Bill received Royal Assent on 13th August 2018. The Welsh Government is also committed to the World Health Organisation Blood Born Virus (WHO BBV) elimination target of 2030(46).

To improve early detection of liver disease, an LFT pathway incorporating up-front "reflex" fibrosis risk assessment is nearing completion and a national liver registry has been introduced to provide high quality health intelligence and inform service provision. Finally, all Health Boards in Wales are now signed up to the IQILS scheme which will act as a strong driver for service improvement. Encouragingly, since 2014 there has been an increase in whole time equivalent (WTE) consultant Hepatologists from 3·7 to 9·5.

Conclusion

There is now a much greater appreciation as well as increasing hard evidence reinforced in this report, of the extent of the disease burden and financial costs resulting from preventable, lifestyle related conditions, particularly liver disease and the complications of cirrhosis including primary hepatocellular carcinoma, along with those related to obesity, namely diabetes, hypertension, chronic kidney disease. Increased risk of the 10 most common cancers is also notable. Despite this, effective fiscal measures for reducing overall alcohol consumption in the

country, namely the duty escalator and Minimum Unit Price policy, have still not been accepted by the English Government. A recent report on student drinking is also of note, putting forward the need to develop an alternative culture to the 'strong man syndrome'(92) if harmful levels of alcohol consumption are to be avoided.

In controlling obesity, levies on sugar content of food as well as on sugary drinks need to be introduced, having been shown to be effective in a number of countries worldwide. The introduction of a strengthened Child Obesity Plan is welcomed and makes a strong case for one for adults. With Scotland having a far-reaching health policy and with Wales introducing measures to control obesity as well as the MUP next year, England is being left a long way behind.

What is also disappointing is that despite all the information available on lifestyle and with considerable media attention including a well-known television and radio presenter who had previously classed himself as a social drinker, going public with details of his own consumption and health impact(93), the general public are apparently not accepting, at least widely, the individual need to control weight and alcohol consumption. Case studies of local initiatives around the country have shown just what can be achieved when public support is obtained. With the NHS facing an aging population, evidence that more years of healthy living are obtainable when diseases can be prevented earlier, has to remain high on the agenda.

Contributors:
RW was responsible for planning and providing content for the Introduction and Conclusion, and writing, editing and overall direction of the paper. ND was responsible for coordinating content and editing. GA, AB contributed to the section on hepatocellular carcinoma. NBh, NBo, DT, JVe, JW contributed with literature searches, data analysis, interpretation and editing. KB, IG, CH, KM, CD, NS, AY contributed to the section on alcohol services. AD, DK contributed to the section on paediatric liver services. GF contributed to the section on viral hepatitis. JG contributed to the section on financial impacts. RA, JDi, HJ, JM, NS contributed to the section on primary care. RB, MM, JVe contributed to the section on public awareness and industry lobbying activities. RB, PN, HR contributed to the section on obesity. MEC, JDy, JF, MH, JOG, LR, NS contributed to the section on hospital services and liver transplantation. CD, JDi, AM, NM, PR, AY contributed to the section on progress in the devolved nations. JVo contributed to the section on attributable cancers.

Acknowledgements:
We thank all those who attended meetings of the working groups of the Commission including Jemma Day (King's College Hospital); Richard Gardner (British Society of Gastroenterology); Maddy Farnworth, Thomas Stephens (Incisive Health); Lynda Greenslade (Royal Free Hospital); Jake Mann (University of Cambridge); Petra Meier (Sheffield Alcohol Research Group, University of Sheffield); Zulfiquar Mirza (Chelsea and Westminster Hospital NHS Foundation Trust); Alastair O'Brien (University College London Hospital); Matthew Parry (www.drfoster.com); Judi Rhys (British Liver Trust); Stephen Ryder (Nottingham University Hospitals NHS Trust); Jeremy Shearman (Royal College of Physicians); Alison Taylor (Children's Liver Disease Foundation); Jeremy Thompson (Fulcrum Practice, Middlesbrough); Indra van Mourik (Birmingham Women's and Children's Hospital); Laura Webber (UK Health Forum and the London School of Hygiene and Tropical Medicine). We thank Norgine for their unrestricted grant to the Foundation for Liver Research which has enabled the Commission to work with Incisive Health in bringing the work of the Commission to the attention of Parliament and in producing the report on *"Understanding the Importance of Living Well for Longer"*. Colin Drummond is part funded by NIHR CLAHRC South London at King's College Hospital NHS Foundation Trust, the NIHR South London and Maudsley NHS Foundation Trust Biomedical Research Centre, and is in receipt of a NIHR Senior Investigator Award. The views expressed are those of the authors and not necessarily those of the NHS, NIHR or the Department of Health.

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